REMARKS

Applicants' again want to thank the Examiner for the courtesy of conducting an interview with applicants' representative on August 10, 2004.

Attached is a copy of the published application US 2002/0051778 A1 and pages 3, 4, 5, 7, 8, 9, 10 and 11 of the application as filed which show in manuscript the amendments which according to our file are being made at this time or were made earlier in prosecution of this application. It is respectfully requested that the copy of the specification in the PTO file be reviewed to ensure that these minor amendments which involve changing one word to another have been entered.

Claims 1, 2, 4, 6 and 7 are in this application. Claims 1, 2, 4, 6 and 7 have been amended as discussed below. Claims 8 and 9 have been cancelled. The subject matter of Claims 8 and 9 have been incorporated into Claim 2.

During the telephone interview the Examiner agreed that she would rejoin the claims for the complex preparation with the claims for the method for treatment of a malignant neoplasm if the claims were amended as set out in this amendment. The Examiner stated during the interview that if the claims were amended to define:

1. a method of treatment of a malignant neoplasm expressing alpha-fetoprotein comprising injecting a complex preparation comprising alpha-fetoprotein, amphotericin B or nystatin and a polysaccharide filler or glucose and
2. a complex preparation comprising alpha-fetoprotein, amphotericin B or nystatin and a polysaccharide filler or glucose

that it appeared that the claims would be allowable pending an interference search.

Claims 1, 2 and 7 were amended to replace the phrase "polyene antibiotics" with amphotericin B and nystatin. This is supported *inter alia* at page 4, line 29 of the originally filed specification. Applicants preserve all rights to file one or more divisional applications which include claims where the polyene antibiotics are not limited to amphotericin B and nystatin.

Support for a malignant neoplasm expressing alpha-fetoprotein receptor is found *inter alia* on page 1, lines 28-31 of the specification.

In the Official Action of March 30, 2004, the Examiner rejected Claim 4 because according to the Examiner there is no support in the specification for polyglucin and rheopolyglucin.

The Examiner stated that she has not considered RU 2179 452 C1 because an English language translation had not been filed. Attached is a certified translation of the priority application RU 2 179 452 (Appendix 1), a copy of the first page of the publication of RU 2179 452 in Russian (Appendix 2) and in English (Appendix 3). Both first pages include abstracts which were prepared by the Russian Patent Office.

The text of RU 2179 452 C1 is essentially, with the exception of the text of the abstract, identical to the text of the patent application as originally filed (some clerical corrections have been made such as deletion of some commas and deletion of the abbrevation No. after the words bulletin and the patient record). In the translated text the spelling used for

the fillers in question is polyglukin and rheopolyglukin based on the respective usage of the terms in the abstract in English prepared (like the abstract in Russian) by the Russian Patent Office. In the English language abstract of RU 2 179 452 C1 the spelling polyglukin and rheopolyglukin has been used as a translation of the corresponding words in the Russian text.

The terms polyglykine and rheopolyglykine are not the names used in the laboratory. The spelling polyglykine and rheopolyglykine presented in the patent application as originally filed in the US PTO is the result of an incorrect translation of the Russian spelling used for the fillers in question.

A search for the words polyglykine, rheopolyglykine, polyglukin, rheopolyglukin, polyglucin and rheopolyglucin to clarify the problem with the spelling of the terms in English using the search engines, GOOGLE, GOOGLE PubMed, Alta Vista, Excite and Teoma gave the following results:

> Only one article in GOOGLE ⇒ PubMed can be found in connection with *polyglykine* (the PubMed abstract included, Appendix 4) and none in connection with *rheopolyglykine.*

This is the same article as indicated by the Examiner in Exhibit 1, page 1 - AB of the Official Action of March 30, 2004. The article is in Russian. A copy of page 1 of the article received over Interlibrary Loan from the University of Helsinki has been enclosed for illustration, underlining the corresponding terms in Russian and in English (Appendix 5). According to the Russian spelling it is evident that this article relates to the same substance, the English spelling of which is *polyglukine.*

The result of the search for the key words polyglukin, rheopolyglukin, polyglucin and rheopolyglucin on the day of the search was as follows:

polyglukin - GOOGLE (11), GOOGLE ⇒ PubMed (7), AltaVista (2), Excite (6), Teoma (1);

rheopolyglukin - GOOGLE (14), GOOGLE ⇒ PubMed (5), AltaVista (4), Excite (9), Teoma (4).

polyglucin - GOOGLE (46), GOOGLE ⇒ PubMed (17289), AltaVista (15), Excite (20), Teoma (11);

rheopolyglucin - GOOGLE (38), GOOGLE ⇒ PubMed (17249), AltaVista (14), Excite (22), Teoma (28);

On the basis of the search the terms *polyglykine* and *rheopolyglykine* seem to be incidental wrong terms in data bases. At the same time it appears that the spelling *polyglucin/polyglukin* and *rheopolyglucin/rheopolyglukin* exist in parallel to define the same dextrans in English. The spelling *polyglucin* and *rheopolyglucin* is predominantly accepted. The spelling *polyglukin* and *rheopolyglukin* is used, with a few exceptions, in the Russian sources. At the same time the Russian authors often use the spelling *polyglucin* and *rheopolyglucin* in their articles as well.

The search in the Russian data bases has been conducted as well. The register of medicinal agents of Russia (**rls** - the abbrevation in English), unfortunately only in Russian, is

available at the address **http://www.rlsnet.ru/opisdrug/**, wherein next to the trade names in Russian the names *polyglucinum* and *rheopolyglucinum* in Latin are presented (please kindly find the corresponding web sites, Appendices 6A and 7A, and the translations of the essential paragraphs thereof, appendices 6B and 7B).

On another Russian information site of pharmaceutical agents at the address / (over GOOGLE) surprisingly *the spellings polyglucin* and *rheopolyglukin* are presented in parallel as the spelling of these dextrans in English (please kindly find the corresponding web sites, Aappendices 8A and 9A, and the translations of the essential paragraphs thereof, Appendices 8B and 9B).

On the basis of the above information and the materials enclosed it is evident that the terms *polyglykine* and *rheopolyglykine* in the patent application as filed with USPTO are incorrect, resulting from the wrong translation from Russian, and do not define the fillers used. Applicant therefore respectfully requests the Examiner to accept the spelling *polyglucin* and *rheopolyglucin* for the fillers in question.

It is respectfully requested that the rejection of Claim 4 be withdrawn.

The fillers in Claims 1, 2, 4, 6 and 7 are defined as polysaccharide fillers and glucose. Support for this is found *inter alia* on page 4, lines 32-34 of the originally filed specification. Glucose is included separately because it is not a polysaccharide.

Applicant respectfully request the Examiner to accept the correction of the incorrectly calculated mass ratio 1:(60-100):(50-70) to the correct ratio *1:(28-100):(23-71)*.

The incorrect mass ratio, disclosed in the description on page 5 lines 8-10, is the result of incorrect calculation of this ratio from the correct quantitative ranges of AFP, a polyene antibiotic and a filler, disclosed in the description on *inter alia* page 4, lines 23-27; on page 5, lines 2-4 and 15-17; on page 6, lines 25-26, on page 7, lines 9-12, and in Claim 2 as originally filed.

The complex preparation comprises the following components, in mg.:

AFP 0.07-0.15

a polyene antibiotic 4.2-7.0

a filler 3.5-5.0

The correct mass ratio is *1:(28-100):(23-71)*, which has been calculated in the following way:

The complex preparation with the lowest quantity of AFP may be calculated as follows:

0.07 : (4.2-7.0) : (3.5-5.0), i.e. 1 : (60-**100**) : (50-**71**),

and with the highest quantity of AFP as follows:

0.15 : (4.2-7.0) : (3.5-5.0), i.e. 1 : (**28**-47) : (**23**-33).

Therefore the correct mass ratio of the complex preparation is:

1 : (28-100) : (23-71).

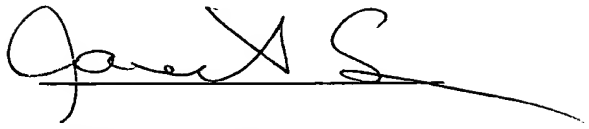
The term *dextran* is a general term that covers the dextrans *polyglucin* and *rheopolyglucin* , and therefore Claims 4 and 6 have been amended to recite "*dextran 100*". This is supported by Example 3.

Submitted herewith are two Declarations of Vladimir Pak. In one Declaration Dr. Pak declares that no complications have resulted from the use of dextrans in Reducin. The other Declaration includes examples that establish that the complex preparations of this invention can be used to treat stomach cancer, breast cancer, ovarian cancer and testicular cancer.

Applicants submit that the present application is in condition for allowance and favorable consideration is respectfully requested.

If any issues remain it is respectfully requested that the Examiner contact the undersigned.

Respectfully submitted,



JANET I. CORD
LADAS & PARRY
26 WEST 61ST STREET
NEW YORK, NEW YORK 10023
REG.NO.33778(212)708-1935

ultrafluid is used. 20 minutes prior to that a dose of 2-10 mg of AFP in 12-15 ml of physiological salt is injected into the liver artery; the repeated treatment is carried out after 3-4 weeks (Patent RU No. 2,065,307, cl. A 61 K 38/17, published August 20, 1996, Bulletin No. 23).

The disadvantages of the known method are:

- labour-intensity of the method, connected with separated injection of AFP and of doxorubicin-estrone complex;
- the use of high concentrations of the chemical preparations (AFP - 2-10 mg, doxorubicin-estrone complex – 20-60 mg), which can lead to toxic side reactions;
- high cost of treatment.

The closest complex preparation to the present complex preparation - the prototype - is a kit used for treatment of primary liver cancer and comprising doxorubicin-estrone in an amount of 20-60 mg in 15 ml vials, Lipiodol ultrafluid in two ampules by 10 ml, AFP in an amount of 2-10 mg in 10 ml vials, physiological salt in volume of 15 ml in an ampule and 96% ethyl alcohol in volume of 5 ml in an ampule (Patent RU No. 2,065,307, cl. A 61 K 38/17, published August 20, 1996, Bulletin No. 23).

The disadvantages of the known kit are:

- labour-intensity and duration of obtaining the sterile doxorubicin-estrone complex as well as labour-intensity of preparation of the working solution of the given preparation: the preparation is dissolved in 0.5-1.5 ml of 96% ethyl alcohol, heating to 70-76°C, the resultant solution is transferred into 10-15 ml of previously upwarmed Lipiodol ultrafluid, the suspension thus obtained is cooled to 32-37°C and is then injected into the liver artery under X-ray television control;
- high concentrations of the preparations used in the kit;

- polycomponent nature of the kit.

The technical object of the group of the inventions is to simplify the known method, to lower the doses of the preparations to be injected and to reduce the costs of treatment.

The established object has been achieved by means of hereby proposed method of treatment of malignant neoplasms and a complex preparation having ~~neoplastic~~ antineoplastic activity for use in such treatment.

The realization of the method of treatment.

Depending on the character and seriousness of the disease, to a patient, together with the basic infusion-detoxication therapy, the complex preparation, comprising AFP in an amount of 0.07-0.15 mg, a polyene antibiotic in an amount of 4.2-7.0 mg and a pharmaceutically suitable filler, is parenterally injected once within twenty-four hours at an interval of three days in a course of 10 infusions.

The complex preparation having antineoplastic activity comprises the following components, in mg:

AFP	0.07 - 0.15
a polyene antibiotic	4.2 - 7.0
a filler	3.5 - 5.0

As a polyene antibiotic amphotericin B or nystatin is mainly used.

As a filler sugars are mainly used, for example glucose or synthetic polymers, selected from the group of polysaccharides, for example ~~polyglykine~~ polyglucin, ~~rheopolyglykine~~ rheopolyglucin and dextran 100.

The complex preparation is obtained as follows: AFP with purity

not less than 98% is dissolved in distilled water or physiological salt in an amount of 0.07-0.15 mg/ml, whereto a polyene antibiotic in an amount of 4.2-7.0 mg/ml and then a filler in an amount of 3.5-5.0 mg/ml are added, after that the components are carefully mixed and the resultant mixture is then left to stand at 18-25°C for 10-12 hours. Thereafter the solution is sterilized by filtration, pre-packed in ampules or vials having a capacity of 1.2 or 3 ml and freeze-dried. The mass ratio of AFP, a polyene antibiotic and a filler is 1 : ~~(60-100)~~ : ~~(50-70)~~. (28-100) : (23-71)

The complex preparation (conventional designation Reducin) is a powder of yellow colour, soluble in water, in physiological salt, in glucose solution and in other diluents (carriers), suitable for intravenous injection. One ampule of the complex preparation comprises: 0.07-0.15 mg of AFP, 4.2-7.0 mg of polyene antibiotic and 3.5-5.0 mg of corresponding filler. For preparation of the working solution the content of the ampule is dissolved in 2-3 ml of sterile water and is then transferred into 200 ml vial together with a carrier, suitable for intravenous injection.

The present method comprises injection to a patient of a new complex chemical preparation having antineoplastic activity and consisting of a vector part (AFP), specific to cancerous cells, and a nonspecific part, comprising a cytotoxic substance. As the latter an essentially new channel-forming and surface-active agent (SAA), namely a polyene antibiotic, for example amphotericin B or nystatin, which have not been previously used as antineoplastic remedies, is used. The targets for the new complex preparation are membranes of intracellular substructures. Such substructures include mitochondria, lysosomes, endoplasmatic reticula (EPR), nuclei, etc. In case of disorders in the function of membranes of substructures, a normal cell function, ensurable by the compartmentalization of different functions, is impossible. As

active agent, namely a polyene antibiotic, mainly amphotericin B or nystatin, in an amount of 4.2-7.0 mg, which provides the complex with a new type of bond with a vector part - with a noncovalent bond, and a new mechanism of interaction with cancerous cells - with the membranes of the substructures of cancerous cells (membranes of lysosomes, EPR, mitochondria, nuclei), which, in its turn, improves the efficiency of the treatment and reduces side complications;

- the complex preparation comprises the components in optimal, experimentally selected amounts and ratios, namely: AFP - 0.07-0.15 mg, a polyene antibiotic - 4.2-7.0 mg, a filler - 3.5-5.0 mg, which enables to improve the efficiency of the treatment and substantially lower the doses of the active components used.

Being supported by the fact that no analogous method of treatment of malignant neoplasms and no analogous complex preparation having antineoplastic activity have been revealed, it may be concluded that the present group of inventions meet the requirements for patentability in respect of "novelty" and "inventive step".

The present method has been tested on 8 patients having IV clinical stage of oncological diseases, progressing after traditional ways of treatment. A full or a partial clinical effect has been achieved on 6 patients out of 8 (75%). The terms of remission were from 6 months to 1.5 years. In majority cases, for achieving a well-defined clinical effect it was sufficient to conduct one course of treatment.

The inventions are characterized by the following Examples.

Example 1

For preparation of the complex preparation Reducin 700 mg of AFP, 42 g of amphotericin B and 50 g of ~~rheopolyglykine~~ rheopolyglucin are dissolved in 1 litre of distilled water by mixing, subsequently

the volume is increased up to 10 litres. The resultant mixture is incubated at room temperature for 10-12 hours and is then subjected to sterilization by filtration through a membrane filter, pre-packed in 10,000 ampules or vials by 1 ml (a single dose) and thereafter freeze-dried in aseptic conditions. One ampule (vial) comprises 0.07 mg of AFP, 4.2 mg of amphotericin B and 5.0 mg of ~~rheopolyglykine~~ rheopolyglucin.

Example 2

The complex preparation Reducin is obtained analogously to Example 1, with the exception that to water solution 1 g of AFP, 50 g of amphotericin B and 40 g of ~~polyglykine~~ polyglucin are added. As a result the preparation, comprising 0.1 mg of AFP, 5.0 mg of amphotericin B and 4.0 mg of ~~polyglykine~~ polyglucin in a single dose, is obtained.

Example 3

The complex preparation is obtained analogously to Example 1, with the exception that to water solution 1.5 g of AFP, 70 g of amphotericin B and 30 g of dextran (molecular mass 100 kDa, Serva) are added. As a result the preparation, comprising 0.15 mg of AFP, 7.0 mg of amphotericin B and 3.0 mg of dextran in a single dose, is obtained.

Example 4

The complex preparation is obtained analogously to Example 1, with the exception that to water solution 750 mg of AFP, 60 g of nystatin and 50 g of glucose are added. As a result the preparation, comprising 0.075 mg of AFP, 6.0 mg of nystatin and 5.0 mg of glucose in a single dose, is obtained.

Example 5

Patient ~~Volnaja~~ L., 54 years old, the patient record No. 587, was hospitalized on April 02, 1999 with the diagnosis: central cancer of the right lung IV stage (recidivation, progressive course), cancer of the left mammary gland II stage (remission). The patient was complaining weakness, dyspnea, exhausting cough.

The data of the inspection. X-ray photograph of the organs of thorax: on both sides in the lungs there are numerous polymorphous shadows of metastases in sizes from 0.5 to 2.5 cm and of medium intensity and uneven outlines. The shadow of mediastinum has shifted rightwards and expanded. The right lung field has diminished in volume; below the fourth rib there is an intensive overshadowing because of the liquid in the pleural cavity.

A course of polychemotherapy was conducted according to the scheme CAF: On the 1^{st} and 8^{th} days intravenously 1 g of cyclophosphane, on the 1^{st} and 8^{th} days intravenously 500 mg of 5-fluorouracil, on the 2^{nd} and 9^{th} days of the treatment intravenously 40 mg of adriablastin. The treatment was accompanied by high toxicity without an expressed clinical effect.

Thereafter the patient was treated according to the present method.The complex preparation Reducin, comprising 0.07 mg of AFP, 4.5 mg of amphotericin B and 5.0 mg of glucose, was injected by infusion in a course of 10 injections once in three days. The condition of the patient has improved and became satisfactory a week after the course of treatment had been finished. On the basis of the data of the radiology inspection of the organs of thorax favourable changes were registered, characterized by the decreased number of metastases in the lungs and the weakening of intensity of the shadows of dissemination. The liquid in the pleural cavity was not inspected. Dyspnea on ascent has diminished and cough disappeared completely. During

the treatment with Reducin a rise in temperature and a shiver were observed, which were treated with standard preparations.

Example 6

Patient Volynyj M., 62 years old, the patient record No. 800, was hospitalized with the diagnosis: central cancer of the right lung IV stage (adenocarcinoma); spread metastases in head, in the right hemisphere of brain, in neck, in thorax; right-sided carcinomatous pleurisy; chronic deforming bronchitis; pulmonary emphysema; diabetes of the 2nd type; IBO; angina of efford; secondary immunodeficiency, undernourishment, condition after the courses of polychemotherapy.

The treatment program included a course of polychemotherapy according to the scheme CAMF. To the patient were injected 1 g of cyclophosphane on the 1^{st} and 8^{th} days, adriamicin on the 1^{st} and 8^{th} days, 50 mg of methotrexate on the 1^{st} and 8^{th} days, 5-fluorouracil on the 2^{nd} and 9^{th} days. The treatment was accompanied by endotoxicosis and an abrupt worsening of the condition of the patient. No positive effects were detected.

Because of complicated condition of the patient, to him intravenous infusions of the complex preparation Reducin, comprising 0.075 mg of AFP, 5.0 mg of nystatin and 5.0 mg of ~~rheopolyglyukine~~ Reopolyglucin in a single dose, in a course of 10 infusions once in three days were prescribed.

6 days after the beginning of the treatment according to the present method the diminishing of the sizes of subcutaneous metastases were noted. By the end of the treatment rapid improvement of the main disease was noted, which became apparent from the twofold reduction of the size of all surface metastatic nodes, the disappearing of pains in the lower jaw, the decreasing of the rate of exudation in the right pleural cavity. Thrice conducted right-sided pleural punction proved the decreasing of

volume of exudate: before the treatment the volume of exudate was 600 ml, a week after the treatment - 350 ml, three weeks after the treatment - 20 ml. The improvement of function of central nervous system became apparent from restoration of normal swallowing function, restoration of gripping function of the left hand, clinically corresponding to the reduction of metastasis in the right hemisphere of brain.

The use of the present method of ~~treatmet~~ treatment of malignant neoplasms and the complex preparation having antineoplastic activity, as compared with the known method of treatment and the kit for use in such treatment, enables:

- to simplify the method of treatment by means of simultaneous parenteral injection of the complex preparation, comprising AFP and cytotoxic SAA in optimal ratios;
- to lower the doses of the used components: AFP 13-140 times, the cytotoxic component 3-14 times;
- to improve the efficiency of treatment by means of using the complex preparation having high specifity to growing cancerous cells and optimal composition of the complex preparation having a long term of storage (two years);
- to reduce the costs of treatment by means of using a small number of components in the complex preparation and low doses of the chemical preparations to be used.

Thus, while using the present method of treatment of malignant neoplasms two biological mechanisms are realized. The first of them comprises the targeted delivery of the cytotoxic agent by means of AFP to tumorous cells. The second one comprises the directed destruction of the tumorous cells because of destruction of the intracellular structures, in particular EPR and lysosomes. This may be accompanied by autodigestion of tumorous cells, caused by the enzymes of hydrolysis, comprising in the lysosomes, according to the mechanism of targetably induced apoptosis. The directed reduction affects much less the cells of blood-forming,